Commentary

Stockwell et al. response: Moderate use of an "intoxicating carcinogen" has no net mortality benefit—is this true and why does it matter?

We thank our commentators for their thoughtful insights, questions, and criticisms of our article (Stockwell et al., 2016—this issue).

Connor (2016) highlights well-substantiated concerns over the validity of conclusions based on observational longitudinal studies of health in general, noting instances in which randomized controlled trials have disconfirmed conclusions based on meta-analysis of cohort studies (e.g., hormone replacement therapy). Greenfield (2016) notes how few cohort studies on the link between alcohol use and mortality take account of the patterning of drinking, whether over weeks, months, or a lifetime. Rehm et al. (2016) suggest that although analysis of alcohol and all-cause mortality from published studies holds interest especially at a political level, in practice they recommend different types of studies on which to base estimates of the global burden of disease and low-risk drinking guidelines. We have also received other comments that we will address briefly here.

We accept these and other limitations. Any meta-analysis is only as good as the quality of the available studies—and the criteria applied to assess variations in their quality. Our vision was to explore what happened to the J-shape curve when meta-analysis is conducted with and without adjustment for the presence of a few empirically and theoretically derived methodological concerns. We focused especially on the effects of contamination of the all-important "abstainer" reference group, against which the health of all other categories of drinkers is usually compared in these studies. There are strong empirical and theoretical grounds for exploring the effects of abstainer group biases. In answer to Greenfield's question about how extensive these problems were in previous meta-analyses and, in particular, that by Ronksley et al. (2011), these have been detailed elsewhere (Stockwell et al., 2012). Among the 84 studies in their review of alcohol and cardiovascular disease as well as all-cause mortality, only 21 excluded former drinkers from the abstainer reference group, and only 16 had also excluded occasional drinkers. Further, we found only two studies in the Ronksley et al. (2011) meta-analysis that met a set of other basic quality criteria. The varying and overall poor quality of this literature motivated our study to investigate how adjusting for study quality can influence observed outcomes.

Turning to criticisms of our own study methods, one reviewer took issue with our definition of what constitutes "low-volume" alcohol consumption. We defined this as at least one 10 g standard drink per week and up to an average of two drinks per day. At the lower end, one drink per week could be considered "homoeopathic," but we note that (a) we had a separate category of an even more homoeopathic level of drinking, namely less than one drink per week; (b) in our pooled analysis, we found the same level of reduced mortality risk for these "occasional" drinkers as for the low-volume drinkers; and (c) as it is, most studies in this literature combine these very low drinking levels into a larger category of moderate drinking. Indeed, Greenfield comments that occasional ("homeopathic") drinkers having the same protection as moderate drinkers is a strong ground for skepticism about the biological plausibility of the idea that alcohol accounts for net mortality benefits observed for moderate drinkers.

It has also been pointed out that our definition of low-volume drinking is not consistent with the U.S. Dietary Guidelines (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010). Our reference point for this definition (supported by Greenfield) was Australia's low-risk drinking guidelines (National Health and Medical Research Council of Australia [NHMRC], 2009) developed by the leading scientists including Robin Room and Jürgen Rehm. It has also been suggested that our applying the same definition of low-volume drinking to males and females is a weakness. However, we note that (a) Australia's guidelines provide the same advice for males and females and (b) we needed to keep a standard definition because we were interested in identifying gender differences in the pattern of results. We found none and hence report findings for men and women combined.

Rehm et al. (2016) also argue that we draw on a literature that is so methodologically deficient and globally unrepresentative that it should not be used as a base either for estimates of the global burden of disease or for devising low-risk drinking guidelines. We did indeed discuss

implications of our findings for drinking guidelines, partly because meta-analyses of alcohol and all-cause mortality have on several occasions been featured as the basis for the levels chosen (e.g., NHMRC, 2001; Stockwell et al., 2012). We agree, however, that there is much shaky and uncertain ground upon which both guidelines and the burden of disease have been estimated. We also agree that there is much interest in attempts to estimate the net effects of alcohol on mortality and that this is part of a larger debate about the role of alcohol in society. Meta-analyses of alcohol and all-cause mortality have played an important role in this and are frequently cited (e.g., Fillmore et al., 2006; Ronksley et al., 2011). We suggest that it is still of interest to explore the validity and replicability of the famous J-shaped curve in this literature under different conditions. Unlike Rehm et al., however, we also suggest that the same uncertainty applies to research on the impact of light drinking on biological markers for cardiovascular disease. They cite evidence of beneficial effects of light drinking on platelets and high-density lipoprotein (HDL). However, the significance of HDL as a biomarker for cardiovascular disease is now under question (Voight et al., 2012). Furthermore, other more proximal markers of cardiovascular risk, such as carotid intima media thickness, are positively associated with even low levels of alcohol consumption (Juonala et al., 2009). Shakiness of the J-shape curve in observational studies is just one component of a growing list of reasons to be skeptical about alcohol's hypothesized health benefits when used in moderation (Chikritzhs et al., 2015).

Among the most thought-provoking comments we felt was Connor's question as to why clinical practice or policy should be influenced by the idea that "an intoxicating, addictive, toxic, carcinogenic drug" such as alcohol could be recommended as a therapeutic agent. In our experience, this clear-sighted perspective is rarely evident among high-level decision-makers, and we have observed policymakers hesitate to introduce effective alcohol policies, or even to support the addition of warning labels on alcohol containers, for fear they might undermine or contradict possible health benefits of alcohol use. We are also aware of some clinicians, especially cardiologists, recommending low-volume alcohol use for therapeutic purposes (e.g., Rubin, 2015) and also alcohol industry groups selectively reporting studies finding health benefits to promote their product (e.g., Masterson, 2015). In closing, we suggest it is still important to question the scientific validity of health claims for alcohol, although we agree that there are many other potential criticisms (e.g., Chikritzhs et al., 2015; Fekjaer, 2013) of this literature we could not examine in the present study. Mounting doubts about the validity of alcohol's health benefits are in keeping with Rehm et al.'s (2016) recommendation that drinking guidelines somehow need to convey the challenging idea that "less is better."

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Declaration of Interest

Statement for Tim Stockwell

Ten years ago I received expenses from the then International Center on Alcohol Policy to attend meetings in New York and Belfast. This organization is funded by alcohol industry groups. I no longer accept funds for any purposes from such sources.

I am currently contracted by the Swedish alcohol monopoly, Systembolaget, to conduct an international collaborative study concerning the policy impacts of government alcohol monopolies on health and safety. Systembolaget was set up to limit the profit incentive in providing alcohol to the public and to minimize adverse health and safety consequences.

Three years ago I accepted funds from Lundbeck, a Danish international pharmaceutical company, to attend a meeting to critique research on a drug they had developed for the treatment of alcohol dependence. I received a fee and travel expenses for a half-day meeting. More than 30 years ago I was paid by a grant from the German drug company Merck to conduct a study of a drug they were developing to treat alcohol dependence. This was paid to the Addiction Research Unit, Institute of Psychiatry, University of London, and paid my salary for 1 year.

Statement for Jinhui Zhao

No conflicts of interest to declare

Statement for Timothy Naimi

No conflicts of interest to declare

Statement for Tanya Chikritzhs

No conflicts of interest to declare

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